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(54) **Title:** COMBINATION TREATMENTS FOR PURINOCEPTOR-RELATED DISORDERS

(57) **Abstract:** The present invention provides methods of preventing and treating purinoceptor-related disorders comprising concurrently administering an A1 adenosine receptor antagonist or a P_{2x} purinoceptor antagonist with an at least one additional active agent effective to treat purinoceptor-related disorders. The present invention also provides pharmaceutical formulations suitable for preventing and treating purinoceptor-related disorders.

COMBINATION TREATMENTS FOR PURINOCEPTOR-RELATED DISORDERS

Cross Reference to Related Applications

This application claims the benefit of U.S. Provisional Application Serial No. 60/386,769 filed June 6, 2002, the disclosure of which is incorporated herein by reference in its entirety.

Field of the Invention

This invention relates to methods of use for A_1 adenosine receptor antagonists or P_{2x} purinoceptor antagonists in combination with other treatments for prevention and treatment of purinoceptor-related disorders. The invention also relates to therapeutically useful pharmaceutical formulations.

Background of the Invention

According to the National Heart, Lung, and Blood Institute (NHLBI) from the National Institutes of Health (NIH) and the World Health Organization (WHO), asthma is defined as a chronic inflammatory disorder of the airways associated with airway hyperresponsiveness, airflow limitation which is partially reversible, and respiratory symptoms of wheezing, breathlessness, cough, and chest tightness (National Institutes of Health/NHLBI 1995. Global strategy for asthma management and prevention NHLBI/WHO workshop report March 1993. NIH Publication No. 95-3659. Bethesda MD: US Dept of Heath and National Heart, Lung, and Blood Institute).

In the U.S., "asthma is one of the most common and costly diseases. More than 5% of the U.S. population has asthma and the numbers are growing" (National Center for Environment Health, Centers for Disease Control and Prevention, Asthma prevention program at-a-glance, (1999)). The mortality rate for asthma is increasing, especially in urban areas (National Center for Environment Health, Centers for Disease Control and Prevention, 1999; Addington WW, Weiss KB. Chicago's response to the public health challenge of urban asthma. *Chest* 116:132S-134S (1999)).

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Currently, the treatment of asthma is avoidance of allergens and use of mast cell stabilizers, beta-2 agonists, xanthines (*e.g.* theophylline), anti-histamines, steroids, and leukotriene antagonists. Many of the current treatments, *e.g.* steroids and beta-2 agonists, may produce serious side effects, and as in the case of leukotriene antagonists, are only modestly effective.

Adenosine produces bronchoconstriction in asthmatics when administered as an inhalational challenge, and currently adenosine receptors (ARs) are considered potential therapeutic targets for drug development in asthma, both as "acute reseue" drugs and preventive, maintenance drugs. A respiratory antisense oligonucleotide (RASON) to the human A_1 AR as an inhalational treatment for the prevention of human asthma is currently in clinical trials. Moreover, bamiphylline, a selective A_1 AR antagonist for the human A_1 AR, is used to treat asthma in Europe (Abbrachio MP and Cattabeni F. Selective activity of bamiphylline on adenosine A1 – receptors in rat brain. *Pharmacol Res* 19:537-545 (1987)).

Two large families of purinergic receptors have been characterized as P_1 (adenosine-sensitive) and P_2 (adenosine triphosphate, ATP- sensitive) purinoceptors. Those in the P_1 class have been further divided into four subtypes - A_1, A_{2a}, A_{2b}, and A_3 - based upon pharmacological profile such as binding to selective ligands, signal transduction mechanisms, and molecular sequences. P_1 AR subtypes A_1, A_{2a}, A_{2b}, and A_3 have been cloned in humans, and are coupled via G proteins to a number of intracellular signal transduction pathways, and are expressed in the lung (Marquardt DL. Adenosine. In Asthma, PJ Barnes, MM Grunstein, AR Leff, AJ Woolcock (eds), pp 585-591, Lippincott-Raven Publishers, Philadelphia, PA, 1997).

Activation of A_1 ARs produces slowing of the heart, depression of heart contractility, bronchoconstriction, renal and pulmonary vasoconstriction, proinflammatory cellular effects, sleep induction, and antinociception (Ely SW and Berne RM: Protective effects of adenosine in myocardial ischemia. *Circulation* 85:893-904 (1992); Murray RD and Churchill PC: Effects of adenosine receptor agonists in the isolated perfused rat kidney. *Am J Physiol* 247:H343-H348 (1984); Neely CF, Haile DM, Cahill BE, Kadowitz PJ: Adenosine and adenosine 5'-triphosphate produce vasoconstriction in the feline pulmonary vascular bed by different mechanisms. *J Pharmacol Exp Ther* 258:753-761 (1991); Ali S, Mustafa SJ, Metzger WJ: Adenosine-induced bronchoconstriction and contraction of airway

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smooth muscle from allergic rabbits with late-phase airway obstruction: evidence for an inducible adenosine A_1 receptor. *J Pharmacol Exp Ther* 268:1328-1334 (1993)).

The P_2 subclass of receptors refers to the receptors sensitive to adenosine triphosphate (ATP) and adenosine diphosphate (ADP). Previously, the P_2 receptors have been classified as P_{2x} and P_{2y} (Abbrachio MP and Burnstock G. Purinoceptors: are there families of P_{2X} and P_{2Y} purinoceptors? *Pharmac Ther* 64:445-475 (1994)). Activation of P_{2X} purinoceptors produces vasoconstriction, platelet aggregation, contraction of the urinary bladder and colon, nociception, and release of mediators from macrophages which are important in the pathophysiology of septic shock (Günter Lambrecht. Agonists and antagonists acting at P_{2X} receptors: selectivity profiles and functional implications. *Naunyn-Schmiedeberg's Arch Pharmacol* 362: 34-350 (2000)). Moreover, activation of P_{2X} purinoceptors on immune cells produces cell death by apoptosis (Burnstock G, Overview of P_2 receptors: possible functions in immune cells. *Drug Devel Res* 53:53-59 (2001)). However, the role of ARs in the pathophysiology and pathogenesis of asthma– hyperreactivity of human airways, the inflammatory response to allergens, airway edema, and the development of airway structural remodeling– seen in human allergic asthma is limited.

Many reports suggest that adenosine produces bronchoconstriction in humans by inducing the release of histamine and newly generated mediators from mast cells (Holgate ST. Experimental models of asthma. *Clin Exp Allergy* 29:82-86 (1999); Barnes PJ, Chung KF, Page CP. Inflammatory mediators of asthma: an update. *Pharmacol Rev* 50:515-596 (1998); Mundell SJ, Olah ME, Panettieri, Jr. RA, Benovic JL, Penn RB. Regulation of G protein-coupled receptor-adenylyl cyclase responsiveness in human airway smooth muscle by exogenous and autocrine adenosine. *Am J Respir Cell Mol Biol* 24:155-163 (2001); and Fozard JR and Hannon JP. Species differences in adenosine receptor-mediated bronchoconstrictor responses. *Clin Exp Allergy* 30:1213-1220 (2000)). In addition to mast cells, ARs are present on a number of other cell types which play important roles in the development of acute and chronic asthma, including bronchial smooth musele cells, neutrophils, eosinophils, basophils, lymphocytes, monocytes and macrophages, platelets, endothelial cells, and fibroblasts. However their role in modulating immune and inflammatory responses in acute and chronic human asthma is unclear.

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A_1, A_{2a}, and A_3 ARs have been identified in human monocytes and macrophages (Sajjadi FG, Takabayashi K, Foster AC, Domingo RC, Firestein GS. Inhibition of TNF-alpha expression by adenosine: role of A3 adenosine receptors. *J Immunol*; 156:3435-3442 (1996); Eppell BA, Newell AM, Brown EJ. Adenosine receptors are expressed during differentiation of monocytes to macrophages in vitro. Implications for regulation of phagocytosis. *J Immunol* 143:4141-4145 (1989); Salmon JE, Brogle N, Brownlie C, Edberg JC, Kimberly RP, Chen BX, Erlanger BF. Human mononuclear phagocytes express adenosine A1 receptors. A novel mechanism for differential regulation of Fc gamma receptor function. *J Immunol* 151:2775-2785 (1993)). As a result of these findings, A_2 AR agonists have been implicated in the treatment of inflammatory diseases. *See* U.S. Patent No. 6,232,297 to Linden et al. In human platelets and lung fibroblasts, A_1 and A_{2a} ARs have been identified and inhibit and stimulate adenylate cyclase, respectively (Dionisotti S, Ferrara S, Molta C, Zocchi C, Ongini E. Labeling of A2a adenosine receptors in human platelets by use of the new nonxanthine antagonist radioligand [3H] SCH58261. *J Pharmcol Exp Ther* 278:1209-1214 (1996); Gurden MF, Coates J, Ellis F, Evans B, Foster M, Hornby E, Kennedy I, Martin DP, Strong P, Vardey CJ. Functional characterization of three adenosine receptor types. *Br J Pharmacol* 109:693-698 (1993); Ahmed AH, Jacobson KA, Kim J, Heppel LA. Presence of both A1 and A2a adenosine receptors in human cells and their interactions. *Biochem Biophys Res Commun* 208:871-878 (1995)).

A_1, A_{2a}, A_{2b}, and A_3 ARs have also been identified in human endothelial cells. In human coronary artery endothelial cells, activation of both A_{2a} and A_{2b} ARs stimulates adenylate cyclase (Olanrewaju HA, Qin W, Feoktistov I, Scemama JL, Mustafa SJ. Adenosine A(2a) and A(2b) receptors in cultured human and porcine coronary artery endothelial cells. *Am J Physiol Heart Circ Physiol* 279:H650-H656 (2000)). In human umbilical vein endothelial cells, activation of A_1 ARs stimulates and activation of A_2 and A_3 ARs inhibits stimulant-induced tissue factor expression, respectively (Deguchi H, Takeya H, Urano H, Gabazza EC, Zhou H, Suzuki K. Adenosine regulates tissue factor expression on endothelial cells. *Thromb Res* 91:57-64 (1998)). In human pulmonary artery endothelial cells, activation of A_1 ARs induces the release of thromboxane and IL-6, both of which increase vascular permeability (Neely CF and Batra VK. Lipopolysaccharide binds to and activates A1

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adenosine receptors on human pulmonary artery endothelial cells. *J Endotoxin Res* 8: 263-271 (2002); Zamora CA, Baron DA, Heffner JE. Thromboxane contributes to pulmonary hypertension in ischemia-reperfusion lung injury. *J Appl Physiol* 74:224-229 (1993); Gornikiewicz A, Sautner T, Brostjan C, *et al.* Catecholamines up-regulate lipopolysaccharide-induced Il-6 production in human microvascular endothelial cells. *FASEB J* 14:1093-1100 (2000)). A number of patents propose the use of a specific chemical structure A_1 adenosine receptor antagonists and methods of use of these A_1 adenosine receptor antagonists as cardiotonics, bronchodilators, and biliary anti-spasm agents. *See* U.S. Patent Nos. 4,783,530, 5,032,593, and 3,309,271.

Published U.S. Patent Application 20020058667 proposes A_1 AR antagonist chemical structures, N-6 substituted 7-deazapurines, and their use for treating a disease associated with an A_1 adenosine receptor: cognitive disease, renal failure, cardiac arrhythmias, respiratory epithelia, transmitter release, sedation, vasoconstriction, bradycardia, negative cardiac inotropy and dromotrophy, bronchoconstriction, neutrophil chemotaxis (anti-inflammatory), reflux condition, or ulcerative condition. This patent application also proposes the use of these specific A_1 AR antagonists for therapy for asthma, chronic obstructive pulmonary disease (COPD), allergic rhinitis, or upper respiratory disorder alone or in combination with other agents.

By blocking activation of purinergic receptors, such as A_1 ARs, A_1 AR antagonists offer a novel, dual mechanism of action for the prevention and early treatment of allergic asthma in humans– prevention and treatment of both the bronchoconstriction and acute inflammation without the side effects associated with many current therapies.

Summary of the Invention

According to embodiments of the present invention, the present invention relates to a method of treating purinoceptor-related disorders, comprising concurrently administering an A_1 adenosine receptor antagonist or a P_{2X} purinoceptor antagonist with at least one additional active agent effective to treat purinoceptor-related disorders.

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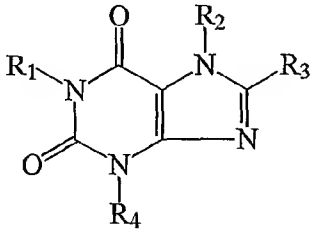
According to other embodiments of the invention, the present invention relates to a method of treating purinoceptor-related disorders, comprising concurrently administering:

(a) an A_1 adenosine receptor antagonist comprising a compound of Formula I:

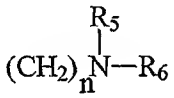


(I)

wherein

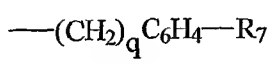
R_1 is selected from the group consisting of C_1-C_8 alkyl;

R_2 is of the formula:



wherein n is an integer ranging from 1 to 8; R_5 is H or $CH_3(CH_2)_p$, wherein p is an integer ranging from 1 to 7; and R_6 is H or $(CH_2)_mOH$, wherein m is an integer ranging from 1 to 8;

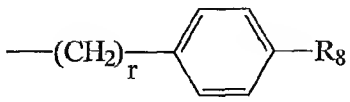
R_3 is of the formula:



and

wherein q is an integer ranging from 1 to 8; and wherein R_7 is selected from the group consisting of H, NH_2, R_9COOH, wherein R_9 is an alkylene or alkenylene group having 1 to 8 carbon atoms, and $(CH_2)_tOH$, wherein t is an integer ranging from 1 to 8; and

R_4 is of the formula:



wherein R_8 is selected from the group consisting of H; NH_2; $(CH_2)_sOH$, wherein s is an integer ranging from 1 to 8; and $R_{10}COOH$, wherein R_{10} is an alkylene

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or alkenylene group having 1 to 8 carbon atoms; and r is an integer ranging from 1 to 8; or a pharmaceutically acceptable salt thereof, or a P_{2x} purinoceptor antagonist or pharmaceutically acceptable salt thereof; with

(b) a compound selected from the group consisting of steroids, *e.g.*, fluticasone, including, but not limited to, fluticasone propionate, beta-2 agonists, *e.g.*, salmeterol, xanthines, *e.g.*, theophylline, A_1 adenosine receptor antagonists, A_{2a} adenosine receptor agonists, A_{2b} adenosine receptor antagonists, A_3 adenosine receptor antagonists, P_{2y} purinoceptor agonists, P_{2x} purinoceptor antagonists, TNF alpha mAb, TNF alpha antagonists, selectin antagonists, beta-2 integrin blockers, interferon, disease modifying anti-rheumatic drugs (DMARDs), proteasome inhibitors, vascular adhesion protein (VAP-1) mAb, neutrophil inhibitory factor, (rNIF), immunomodulators, NHE inhibitors, monophosphoryl Lipid A (MPL A), other immune stimulants, including, but not limited to, mycobacterium, endotoxin, interferon-alpha, granulocyte colony stimulating factor (GCSF), granulocyte-macrophage colony stimulating factor (GMCSF), endotoxin antagonists, antifactor IX mAb, p38 mitogen-activated protein kinase (p38 MAPK) inhibitor, lipid emulsion, platelet activating factor acetylhydrolase (PAF-AH), CD14 receptor antagonist, caspase inhibitors, protease inhibitors, nitric oxide scavengers, nitric oxide blockers, nitric oxide synthetase inhibitors, re tissue factor protein inhibitors (re TFPI), bactericidal permeabilizing increasing re (BPI) protein fragment, CpG DNA, Mycobacterium vaccae, lactobacillus, modified endotoxin – Lipid A, diuretics, vasodilators, anti-platelet agents, anticoagulants, nitrates, calcium channel blockers, beta receptor antagonists, antihypertensives, diuretics, antidepressants, appetite suppressants, mast cell stabilizers, anti-histamines, cetirizine, leukotriene receptor antagonists, anticytokines, phosphodiesterase enzyme inhibitors, 5-lipoxygenase inhibitors, platelet activating factor antagonists, thromboxane receptor antagonists, neurokinin receptor antagonists, central nervous system (CNS) stimulants, cognition enhancers, acetylcholinesterase inhibitors, acridine derivative, for example, tetrahydroaminoacridine (tacrine), complement receptor antagonists, cyclosporin, endothelin receptor antagonists, angiotensin enzyme converting (ACE) inhibitors, antisense oligonucleotides, anti-IgE, insulin, oral hypoglycemics, smooth muscle relaxants, antibiotics, antiviral agents, antifungal agents, anti-inflammatory agents, also including nonsteroidal anti-inflammatory agents, cancer therapies, narcotics,

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antitussive agents, surfactants, and combinations thereof, in an amount effective to treat the purinoceptor-related disorder.

Aceording to still other embodiments of the present invention, the present invention relates to a method of treating purinoceptor-related disorders, comprising concurrently administering an A_1 adenosine receptor antagonist or a P_{2x} purinoeeptor antagonist with at least one additional active agent effective to treat purinoceptor-related disorders, wherein the purinoceptor-related disorder is seleeted from the group consisting of, congestive heart failure, hypertension, such as systemic hypertension and pulmonary hypertension, ischemia-reperfusion organ injury, endotoxin-related tissue injury, renal failure, Alzheimer's disease, depression, obesity, asthma, diabetes, cystic fibrosis, allergic conditions, including, but not limited to allergic rhinitis and anaphylactic shock, autoimmune disorders, inflammatory disorders, chronic obstructive pulmonary disorders, chronic cough, coronary artery disease, biliary colic, postoperative ileus, fibrosis, sclerosis, Adult Respiratory Distress Syndrome (ARDS), Acute Lung Injury (ALI), Severe Acute Respiratory Syndrome (SARS), septicemia, substance abuse, drug dependence, and Parkinson's disease.

A further embodiment of the present invention is the use of an active agent as described above for the preparation of a medicament for the treatment of a disorder as described above.

According to yet other embodiments of the present invention, the present invention relates to the use of active compounds as disclosed herein for the manufacture of a medicament for the prophylactic or therapeutic treatment of asthma in a patient in need of such treatment.

Detailed Description of Preferred Embodiments

The foregoing and other aspects of the present invention will now be described in more detail with respect to other embodiments described herein. It should be appreciated that the invention can be embodied in different forms and should not be construed as limited to the embodiments set forth herein. Rather, these embodiments are provided so that this disclosure will be thorough and complete, and will fully convey the scope of the invention to those skilled in the art.

The terminology used in the description of the invention herein is for the purpose of describing particular embodiments only and is not intended to be limiting

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of the invention. As used in the description of the invention and the appended claims, the singular forms "a", "an" and "the" are intended to include the plural forms as well, unless the context clearly indicates otherwise.

Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs.

All publications, U.S. patent applications, U.S. patents and other references cited herein are incorporated by reference in their entireties.

The term "alkyl" as used herein refers to C1-C20 inclusive, linear, branched, or cyclic, saturated or unsaturated hydrocarbon chains, including for example, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert-butyl, pentyl, hexyl, octyl, ethenyl, propenyl, butenyl, pentyl, hexenyl, octenyl, butadienyl, and allenyl groups. Alkyl groups can either be unsubstituted or substituted with one or more non-interfering substituents, e.g., halogen, alkoxy, acyloxy, hydroxy, mercapto, carboxy, benzyloxy, phenyl, benzyl, or other functionality which has been suitably blocked with a protecting group so as to render the functionality non-interfering. Each substituent may be optionally substituted with additional non-interfering substituents. The term "non-interfering" characterizes the substituents as not adversely affecting any reactions to be performed in accordance with the process of this invention.

The term "alkenylene" denotes groups formed from straight chain, branched or cyclic alkenes including ethylenically mono-, di- or poly-unsaturated alkyl or cycloalkyl groups. Non-limiting examples of alkenyl include vinyl, allyl, 1-methylvinyl, butenyl, iso-butenyl, 3-methyl-2-butenyl, 1-pentenyl, cyclopentenyl, 1-methyl-cyclopentenyl, 1-hexenyl, 3-hexenyl, cyclohexenyl, 1-heptenyl, 3-heptenyl, 1-octenyl, cyclooctenyl, 1-nonenyl, 2-nonenyl, 3-nonenyl, 1-decenyl, 3-decenyl, 1,3-butadienyl, 1-4,pentadienyl, 1,3-cyclopentadienyl, 1,3-hexadienyl, 1,4-hexadienyl, 1,3-cyclohexadienyl, 1,4-cyclohexadienyl, 1,3-cycloheptadienyl, 1,3,5-cycloheptatrienyl and 1,3,5,7-cyclooctatetraenyl.

The term "A_1 adenosine receptor antagonist" as used herein refers to a compound that partially or completely inhibits the activity of an A_1 adenosine receptor agonist.

The term "purinoceptor-related disorder" refers to conditions wherein purinoceptor agonists, for example, nucleosides, such as adenosine, adenosine

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agonists, adenosine triphosphate, or related triphosphate or diphosphate nucleotides, or combinations thereof, play a role in the condition observed.

As used herein, the term "asthma" refers to a chronic inflammatory disorder of the airways assoeiated with airway hyperresponsiveness, airflow limitation which is partially reversible, and respiratory symptoms of wheezing, breathlessness, cough, and chest tightness. Asthma can be divided into two groups: 1) allergic/extrinsic asthma, and 2) intrinsic/non-atopic asthma associated with asthma attacks provoked by exercise, cold, and psychological stress. Allergic asthma is characterized by an acute, early-stage (immediate) allergic response (EAR) and a late-phase (delayed) allergic response (LAR) characterized by airway inflammation, bronchial hyperreactivity, and airway damage which can ultimately progress to fibrosis and structural remodeling of airways (Willis-Karp M. Immunologic basis of antigen-induced airway hyperresponsiveness. Annu Rev Immunol 1999; 17:255-281). Rapid mucosal edema, airway narrowing, and mast cell degranulation characterize the early asthmatic response. Binding of IgE produced by antigen presenting B cells triggers the degranulation of mast cells. The late asthmatic response is characterized by the migration of eosinophils and lymphocytes from the blood into the lung parenchyma and airway epithelium. In both the early and late phase responses, the production of chemotactic factors and cytokines that promote the T lymphocyte type 2 (Th2) immune response, *e.g.* IL-4, IL-5, and IL-13, contributes to the development of airway reactivity and airflow obstruction.

The term "autoimmune disorder" refers to autoimmune disorders or diseases that can be caused by the failure of the immune system to distinguish self from non-self. In these disorders, the immune system reacts against self tissues and this response can cause inflammation and tissue injury. Autoimmune disorders can be classified into two basic categories: (1) antibody-mediated diseases including, but not limited to, systemic lupus erythematosus (SLE), pemphigus vulgaris, myasthenia gravis, hemolytic anemia, thrombocytopenia purpura, Grave's disease, Sjogren 's disease and dermatomyositis; and (2) cell-mediated diseases including, but not limited to, Hashimoto's disease, polymyositis, inflammatory bowel disease, multiple sclerosis, diabetes mellitus, ulcerative colitis, rheumatoid arthritis, and scleroderma. As used herein, an autoimmune disorder may be or have the clinical manifestations of an inflammatory disorder.

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The term "bronchodilating agent" as used herein refers to an agent that prevents, reduces, or reverses the degree of airway constriction. Examples of bronchodilating agents include, but are not limited to, βeta-2 adrenergic agonists, methylxanthines, including, but not limited to theophylline, theobromine, and caffeine, anti-cholinergics, anti-histamines, leukotriene receptor antagonists, and phosphodiesterase inhibitors.

As used herein, the term "anti-inflammatory agent" refers to an agent that prevents or inhibits the signs and symptoms of inflammation. Examples of anti-inflammatory agents include, but are not limited to, glucocorticoids, cromolyn, and nonsteroidal anti-inflammatory drugs. However, it is noted that a "bronchodilating agent" may have anti-inflammatory properties and an "anti-inflammatory agent" may have bronchodilating properties.

The term "treat" as used herein refers to any type of treatment that imparts a benefit to a patient afflicted with a disease, including improvement in the condition of the patient (*e.g.*, in one or more symptoms), delay in the progression of the disease, etc.

As used herein, a treatment effective amount is an amount effective to result in improvement in the condition of the patient (*e.g.*, in one or more symptoms), delay in the progression of the disease, etc.

The term "pharmaceutically acceptable" as used herein means that the compound or composition is suitable for administration to a subject to achieve the treatments described herein, without unduly deleterious side effects in light of the severity of the disease and necessity of the treatment.

As used herein, the word "concurrently" means sufficiently close in time to produce a combined effect (that is, concurrently may be simultaneously, or it may be two or more events occurring within a short time period before or after each other).

As used herein, the administration of two or more compounds "in combination" means that the two compounds are administered closely enough in time that the presence of one alters the biological effects of the other. The two compounds may be administered simultaneously (i.e., concurrently) or sequentially. Additionally, simultaneous administration may be carried out by mixing the compounds prior to administration, or by administering the compounds at the same point in time but at different anatomic sites or using different routes of administration.

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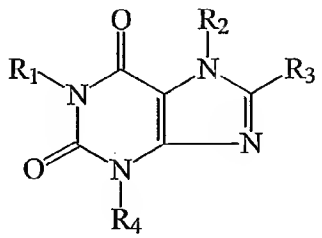
The phrases "concurrent administration," "administration in combination," "simultaneous administration" or "administered simultaneously" as used herein, interchangeably mean that the compounds are administered at the same point in time or immediately following one another. In the latter case, the two compounds are administered at times sufficiently close that the results observed are indistinguishable from those achieved when the compounds are administered at the same point in time.

Suitable subjects to be treated according to the present invention include both avian and mammalian subjects, preferably mammalian. Mammals according to the present invention include but are not limited to canine, felines, bovines, caprines, equines, ovines, porcines, rodents (*e.g.* rats and mice), lagomorphs, primates, and the like, and encompass mammals *in utero*. Humans are preferred. Human subjects of both genders and at any stage of development (*i.e.*, neonate, infant, juvenile, adolescent, adult) can be treated according to the present invention.

Illustrative avians according to the present invention include chickens, ducks, turkeys, geese, quail, pheasant, ratites (*e.g.*, ostrich) and domesticated birds (*e.g.*, parrots and canaries), and include birds *in ovo*. Chickens and turkeys are preferred. Any mammalian subject in need of being treated according to the present invention is suitable. The present invention is primarily concerned with the treatment of human subjects, but the invention may also be carried out on animal subjects, particularly mammalian subjects such as mice, rats, dogs, cats, livestock and horses for veterinary purposes, and for drug screening and drug development purposes.

1. Active compounds.

The methods of the present invention include the administration of compounds of Formula I, while pharmaceutical compositions of the present invention comprise compounds of Formula I. As used herein, a compound of Formula I is as follows:



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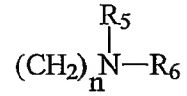
wherein

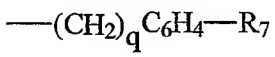
R_1 is selected from the group consisting of C_1-C_8 alkyl;

R_2 is of the formula:



wherein n is an integer ranging from 1 to 8; R_5 is H or $CH_3(CH_2)_p$, wherein p is an integer ranging from 1 to 7; and R_6 is H or $(CH_2)_mOH$, wherein m is an integer ranging from 1 to 8;

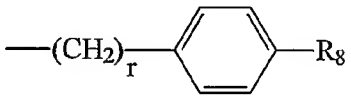
R_3 is of the formula:



and

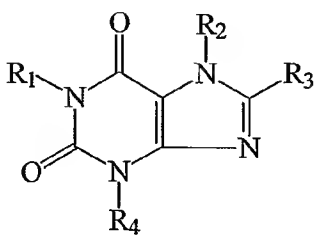
wherein q is an integer ranging from 1 to 8; and wherein R_7 is selected from the group consisting of H, NH_2, R_9COOH, wherein R_9 is an alkylene or alkenylene group having 1 to 8 carbon atoms, and $(CH_2)_tOH$, wherein t is an integer ranging from 1 to 8; and

R_4 is of the formula:



wherein R_8 is selected from the group consisting of H; NH_2; $(CH_2)_sOH$, wherein s is an integer ranging from 1 to 8; and $R_{10}COOH$, wherein R_{10} is an alkylene or alkenylene group having 1 to 8 carbon atoms; and r is an integer ranging from 1 to 8; or a pharmaceutically acceptable salt thereof.

The methods of the present invention also include the administration of a compound of Formula II, while pharmaceutical compositions of the present invention comprises a compound of Formula II. As used herein, a compound of Formula I is as follows:



(II)

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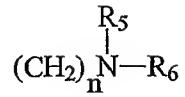
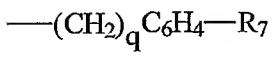
wherein R_1 is C_3 alkyl;

R_2 is of the formula:



wherein n is 2; R_5 is $CH_3(CH_2)_p$, wherein p is 1; R_6 is $(CH_2)_mOH$, wherein m is 2;

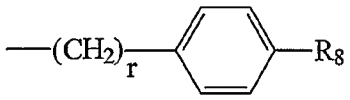
R_3 is of the formula:



and

wherein q is 1; R_7 is H; and

R_4 is of the formula:



wherein R_8 is NH_2; and r is 2; or a pharmaceutically acceptable salt thereof.

The synthesis of the compound according to the Formula I is described in detail in U.S. Patent No.5,786,360 and 6,489,332 to Neely.

The methods of the present invention also include the administration of A_1 receptor antagonists and P_{2X} receptor antagonists. Examples of A_1 receptor antagonists include, but are not limited to, alkyl xanthines such as 8-cyclopentyl-1,3-dipropylxanthine (DPCPX), xanthine amine cogener (XAC), xanthine carboxylic cogener (XCC), 1,3-dipropyl-8-(3-noradamantyl) xanthine (KW 3902), 1,3-dipropyl-8-(dicyclopropylmethyl)xanthine (KF 15372), 1,3-dipropyl-S-(3-oxocyclopentyl xanthine (KFM 19), 1-propyl-3-(4-amino-3-iodophenethyl)-8-cyclopentylxanthine (BW-A844U), 1,3-dipropyl-8-sulfophenylxanthine (DPSPX), cyclopentyl theophylline (CPT) and 7-[2-ethyl (2-hydroxyethyl) amino]-ethyl]-3,7-dihydro-1,3 -dimethyl-8-(phenylmethyl)-1H-purine-2,6-dione (Bamifylline (BAM)), 8-cyclopentyl-3-(3-((-4-fluorosulfonylbenozoyl)-oxy)propyl)-1-propylxanthine (FSCPX), 1,3-dipropyl-8-(3-noradamantyl)xanthine (NAX); 1,3-dipropyl-8-[2(5,6-epoxy)norbornyl]xanthine (ENX), 8-(1(R)-Methyl-2-phenylethyl)-1,3-dipropyl-7H-xanthine (MDL 102503); N^6, 9-methyl adenines such as (±) N^6 -endonorbornan-2-yl-9-methyladenine (N-0861); N^6, 9-disubstituted adenines; 2-phenyl-7-deazaadenines

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such as (R)-7,8-dimethyl-2-phenyl-9-(1-phenylethyl)-7-deazaadenine; 3-(2-substituted-3-oxo-2,3-dihydropyridazin-6-yl)-2-phenylpyrazolo[1,5-α]pyridines, such as 7,8-dihydro-8-ethyl-2-(3-noradamantyl)-4-propyl-1H-imidazo[2,1-i]purin-5(4 H)-one;(±)R-1-[(ε)-3[2-]phenylpyrazolo(1,5-a)pyridin-3-yl]acryloyl]-2-piperidine ethanol; 8-azaxanthines such as 7-cyclopentyl-1,3-dipropyl-8-azaxanthine; pyrazolo[3,4-*c*]quinolines; pyrazolo-[1,5-α]pyridines, such as (E)-R-1-(1-Oxo-3-(2-phenylpyrazolo(1,5-α)pyridin-3-yl)-2-propenyl)-2-pyperidineacetic acid (FK 352), 3-(2-(3-Carboxypropyl)-3-oxo-2,3-dihydropyridazin-6-yl)-2-phenylpyrazolo(1,5-α)pyridine (FK 838), 2-Piperidineethanol, 1-(1-oxo-3-(2-phenylpyrazolo(1,5α)pyridin-3-yl)-2-propenyl)-,(R-(E)) (FK 453) ; 1,8-naphthyridines; (3-phenyl)-1,2,4-thiadiazoles such as *N*-(3-Phenyl-1,2,4-thiadiazol-5-yl)-4-methoxybenzamide (LUF 5417); 4-phenyl-2-(phenylcarboxamido)-1,3-thiazole, *N*-(4-Phenylthiazol-2-yl)-4-methoxybezamide (LUF 5433); 3-Aryl[1,2,4]triazno[4,3-α]benzimidazol-4(10H)ones (ATBIs); Imidazol[1,2-α]quinoxalin-4-amines, such as N-cyclopentylamino-1-methylimidazo(1,2-α)quinoxalin-4-amine (IRFI 165); triazoloquinazolines; 1,2,4-Triazolo[4,3-α]quinoxalin-1-ones; and 2-arylpyrzaolo[3,4-*c*]quinolines.

Examples of P_{2X} receptor antagonists include, but are not limited to, pyridoxalphosphate-6-azophenyl-2',4'-disulfonic acid (PPADS), pyridoxal-5'-phosphate-6-azophenyl]-2',5'-disulfonate (iso-PPADS); α,β-Me ATP; 4,4'-diisothiocyanatostilbene-2,2'-disulphonate (DIDS); isoquinoline sulfonamide 1-[*N,O-bis*(5-isoquinoline-sulfonyl)-N-methyl-L-tyrosyl]-4-phenylpiperazine (KN-62); trinitrophenyl (TNP)-substituted nucleotides (TNP-ATP); diinosine pentaphosphate (IP_5I); PPADS analogs, pyridoxine cyclic phosphate, such as cyclic pyridoxine-α-monophosphate-6-phenylazo-2',5'-disulfonate (MRS 2220) and pyridoxal-5'-phosphate-6-(2'-naphthylazo-6'-nitro-4',8'-disulfonate (PPNDS);suramin; suramin analogues, such as 8-(benzamido)naphthalene-1,3,5-trisulfonate (NF023); 8,8'-(carbonylbis(imino-4,1-phenylenecarbonylimino-4,1-phenylenecarbonylimino))bis(1,3,5-naphthalenetrisulfonic acid (NF279); and 4,4',4'',4''-(carbonylbis(imino-5,1,3-benzenetriyl-bis(carbonylimino)))tetrakis-benzene-1,3-disulfonic acid (NF449).

For the sake of simplicity, Formulas I and II herein illustrate the active compounds in the naturally occurring D configuration, but the present invention also

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encompasses compounds in the L configuration, and mixtures of compounds in the D and L configurations, unless otherwise specified. The naturally occurring D configuration is preferred.

The active compounds disclosed herein can, as noted above, be prepared in the form of their pharmaceutically acceptable salts. Pharmaceutically acceptable salts are salts that retain the desired biological activity of the parent compound and do not impart undesired toxicological effects. Examples of such salts are (a) acid addition salts formed with inorganic acids, for example hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid, nitric acid and the like; and salts formed with organic acids such as, for example, acetic acid, oxalic acid, tartaric acid, succinic acid, maleic acid, fumaric acid, gluconic acid, citric acid, malic acid, ascorbic acid, benzoic acid, tannic acid, palmitic acid, alginic acid, polyglutamic acid, naphthalenesulfonic acid, methanesulfonic acid, p-toluenesulfonic acid, naphthalenedisulfonic acid, polygalacturonic acid, and the like; (b) salts formed from elemental anions such as chlorine, bromine, and iodine, and (c) salts derived from bases, such as ammonium salts, alkali metal salts such as those of sodium and potassium, alkaline earth metal salts such as those of calcium and magnesium, and salts with organic bases such as dicyclohexylamine and N-methyl-D-glucamine.

2. Methods of Use

The present invention provides a method of treating purinoceptor receptor-related disorders, comprising concurrently administering an A_1 adenosine receptor antagonist or a P_{2x} purinoceptor antagonist with at least one additional active agent effective to treat purinoceptor-related disorders. Purinergic compounds which may interact with adenosine receptors include the naturally present adenosine and ATP or the synthetic adenosine analogues, and are well known to exert multiple functions in almost every tissue of the body, but are particularly conspicuous and therefore have been extensively studied in the brain where general antinociceptive (analgesic or even anesthetic), antiepileptic and tissue protective effects are well documented. *See* U.S. Patent No. 6,015,835 to Miyamoto. Purinoceptors have been associated with disorders and conditions cited above and those including, but not limited to, congestive heart failure, hypertension, such as systemic hypertension and pulmonary hypertension, ischemia-reperfusion organ injury, endotoxin-related tissue injury, renal

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failure, Alzheimer's disease, depression, obesity, asthma, diabetes, cystic fibrosis, allergic conditions, including, but not limited to allergic rhinitis and anaphylactic shock, autoimmune disorders, chronic obstructive pulmonary disorders, chronic eough, coronary artery disease, biliary colic, postoperative ileus, fibrosis, sclerosis, septicemia, Adult Respiratory Distress Syndrome (ARDS), Acute Lung Injury (ALI), Severe Acute Respiratory Syndrome (SARS), substance abuse, drug dependence, and Parkinson's disease. It has also been shown that administration of compositions comprising selective A_1 adenosine receptor antagonists and/or P_{2X} receptor antagonists can prevent injuries related to ischemia followed by reperfusion in an organ, and A_1 adenosine receptor antagonists and/or P_{2X} receptor antagonists have been implicated in the prevention and treatment of ischemia-reperfusion and endotoxin-related tissue injuries. *See* U.S. Patent Nos. 6,001,842; 5,733,916; and 5,504,090 to Neely. Administration of compositions comprising selective A_1 adenosine receptor antagonists and/or P_{2X} receptor antagonists have also been implicated in the prevention and treatment of fibrosis and sclerosis. *See* U.S. Patent No. 6,117,445 to Neely.

Thus, the A_1 adenosine receptor antagonists or P_{2X} receptor antagonists compounds, compositions, and formulations of the present invention concurrently administered with at least one additional active agent effective to treat purinoceptor-related disorders as provided in the present invention, provide useful therapeutic methods of preventing and treating purinoceptor-related disorders. Such purinoceptor-related disorders include, but are not limited to, congestive heart failure, hypertension, for example, systemic hypertension and pulmonary hypertension, ischemia-reperfusion organ injury, endotoxin-related tissue injury, renal failure, Alzheimer's disease, depression, obesity, asthma, diabetes, cystic fibrosis, chronic obstructive pulmonary disorders, chronic cough, coronary artery disease, biliary colic, postoperative ileus, fibrosis, sclerosis, autoimmune disorders, allergic conditions, including, but not limited to allergic rhinitis and anaphylactic shock, inflammatory disorders, Adult Respiratory Distress Syndrome (ARDS), including Severe Acute Respiratory Syndrome (SARS) and Acute Lung Injury (ALI), septicemia, substance abuse, drug dependence, and Parkinson's disease.

Agents known to be effective to treat purinoceptor-related disorders can be administered in combination with the compounds and compositions of the present

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invention with the proviso that combination therapies currently known to specifically treat known purinoceptor-related disorders are not contemplated by the present invention. Examples of such agents include, but are not limited to, steroids, *e.g.*, fluticasone, including but not limited to, fluticasone propionate, beta agonists such as beta 2 agonists, *e.g.*, salmeterol, xanthines, *e.g.*, theophylline, A_1 adenosine receptor antagonists, A_{2a} adenosine receptor agonists, A_{2b} adenosine receptor antagonists, A_3 adenosine receptor antagonists, P_{2y} purinoceptor agonists, P_{2x} purinoceptor antagonists, TNF mAb, TNF antagonists, selectin antagonists, beta-2 integrin blockers, interferon, disease modifying anti-rheumatic drugs (DMARDs), proteasome inhibitors, VAP-1 mAb, rNIF, immunomodulators, NHE inhibitors, monophosphoryl Lipid A (MPL A), other immune stimulants, including, but not limited to, mycobacterium, endotoxin, interferon-alpha, granulocyte colony stimulating factor (GCSF), granulocyte-macrophage colony stimulating factor (GMCSF), endotoxin antagonists, antifactor IX mAb, p38 MAPK inhibitor, lipid emulsion, PAF acetylhydrolase, CD14 receptor antagonist, caspase inhibitors, protease inhibitors, nitric oxide scavengers, nitric oxide blockers, nitric oxide synthetase inhibitors, re tissue factor protein inhibitors (re TFPI), bactericidal permeabilizing increasing re (BPI) protein fragment, CpG DNA, Mycobacterium vaccae, lactobacillus, modified endotoxin – Lipid A, diuretics, vasodilators, anti-platelet agents, anticoagulants, nitrates, calcium channel blockers, beta receptor antagonists, antihypertensives, diuretics, antidepressants, appetite suppressants, mast cell stabilizers, anti-histamines, cetirizine, leukotriene receptor antagonists, anticytokines, phosphodiesterase enzyme inhibitors, 5-lipoxygenase inhibitors, platelet activating factor antagonists, thromboxane receptor antagonists, neurokinin receptor antagonists, central nervous system (CNS) stimulants, cognition enhancers, acetylcholinesterase inhibitors, acridine derivative, for example, tetrahydroaminoacridine (tacrine), complement receptor antagonists, cyclosporin, endothelin receptor antagonists, angiotensin enzyme converting (ACE) inhibitors, antisense oligonucleotides, anti-IgE, insulin, hypoglycemics, smooth muscle relaxants, antibiotics, antiviral agents, antifungal agents, anti-inflammatory agents, also including nonsteroidal anti-inflammatory agents, cancer therapies, narcotics, antitussive agents, and surfactants. The compounds and compositions of the present invention can be administered with one

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or more of the agents described above which include analogs thereof and isolated and recombinant forms of the agents.

3. Pharmaceutical formulations.

The active compounds described above may be formulated for administration in a pharmaceutical carrier in accordance with known techniques. *See, e.g.,* Remington, *The Science And Practice of Pharmacy* (9th Ed. 1995). In the manufacture of a pharmaceutical formulation according to the invention, the active eompound (including the physiologically acceptable salts thereof) is typically admixed with, *inter alia,* an acceptable carrier. The carrier must, of course; be acceptable in the sense of being compatible with any other ingredients in the formulation and must not be deleterious to the patient. The carrier may be a solid or a liquid, or both, and is preferably formulated with the compound as a unit-dose formulation, for example, a tablet, which may contain from 0.01 or 0.5% to 95% or 99% by weight of the active compound. One or more active compounds may be incorporated in the formulations of the invention, which may be prepared by any of the well-known techniques of pharmacy consisting essentially of admixing the components, optionally including one or more accessory ingredients.

The formulations of the invention include those suitable for oral, rectal, topical, buccal (e.g., sub-lingual), vaginal, parenteral (e.g., subcutaneous, intramuscular, intradermal, or intravenous), topical (*i.e.,* both skin and mucosal surfaces, including airway surfaces), intraarticular, transdermal, nasal, and inhalational administration, although the most suitable route in any given case will depend on the nature and severity of the condition being treated and on the nature of the particular active compounds which is being used.

Formulations suitable for oral administration may be presented in discrete units, such as capsules, cachets, lozenges, or tablets, each containing a predetermined amount of the active compound; as a powder or granules; as a solution or a suspension in an aqueous or non-aqueous liquid; or as an oil-in-water or water-in-oil emulsion. Such formulations may be prepared by any suitable method of pharmacy which includes the step of bringing into association the active compound and a suitable carrier (which may contain one or more accessory ingredients as noted above). In general, the formulations of the invention are prepared by uniformly and

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intimately admixing the active compound with a liquid or finely divided solid carrier, or both, and then, if necessary, shaping the resulting mixture. For example, a tablet may be prepared by compressing or molding a powder or granules containing the active compound, optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing, in a suitable machine, the compound in a free-flowing form, such as a powder or granules optionally mixed with a binder, lubricant, inert diluent, and/or surface active/dispersing agent(s). Molded tablets may be made by molding, in a suitable machine, the powdered compound moistened with an inert liquid binder.

Formulations suitable for buccal (sub-lingual) administration include lozenges comprising the active compound in a flavoured base, usually sucrose and acacia or tragacanth; and pastilles comprising the compound in an inert base such as gelatin and glycerin or sucrose and acacia.

Formulations of the present invention suitable for parenteral administration comprise sterile aqueous and non-aqueous injection solutions of the active compound, which preparations are preferably isotonic with the blood of the intended recipient. These preparations may contain anti-oxidants, buffers, bacteriostats and solutes which render the formulation isotonic with the blood of the intended recipient. Aqueous and non-aqueous sterile suspensions may include suspending agents and thickening agents. The formulations may be presented in unit\dose or multi-dose containers, for example sealed ampoules and vials, and may be stored in a freeze-dried (lyophilized) condition requiring only the addition of the sterile liquid carrier, for example, saline or water-for-injection immediately prior to use. Extemporaneous injection solutions and suspensions may be prepared from sterile powders, granules and tablets of the kind previously described. For example, in one aspect of the present invention, there is provided an injectable, stable, sterile composition comprising a compound of Formula I or II, A_1 adenosine receptor antagonists or P_{2x} purinoceptor antagonists, or a salt thereof, in a unit dosage form in a sealed container. The compound or salt is provided in the form of a lyophilizate which is capable of being reconstituted with a suitable pharmaceutically acceptable carrier to form a liquid composition suitable for injection thereof into a subject. The unit dosage form typically comprises from about 10 mg to about 10 grams of the compound or salt. When the compound or salt is substantially water-insoluble, a sufficient amount of emulsifying agent which is

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physiologically acceptable may be employed in sufficient quantity to emulsify the compound or salt in an aqueous carrier. One such useful emulsifying agent is phosphatidyl choline.

Formulations suitable for rectal administration are preferably presented as unit dose suppositories. These may be prepared by admixing the active compound with one or more conventional solid carriers, for example, cocoa butter, and then shaping the resulting mixture.

Formulations suitable for topical application to the skin preferably take the form of an ointment, cream, lotion, paste, gel, spray, aerosol, or oil. Carriers which may be used include petroleum jelly, lanoline, polyethylene glycols, alcohols, transdermal enhancers, and combinations of two or more thereof.

Formulations suitable for transdermal administration may be presented as discrete patches adapted to remain in intimate contact with the epidermis of the recipient for a prolonged period of time. Formulations suitable for transdermal administration may also be delivered by iontophoresis (*see*, for example, *Pharmaceutical Research* **3 (6)**:318 (1986)) and typically take the form of an optionally buffered aqueous solution of the active compound. Suitable formulations comprise citrate or bis\tris buffer (pH 6) or ethanol/water and contain from 0.1 to 0.2M active ingredient.

Further, the present invention provides liposomal formulations of the compounds disclosed herein and salts thereof. The technology for forming liposomal suspensions is well known in the art. When the compound or salt thereof is an aqueous-soluble salt, using conventional liposome technology, the same may be incorporated into lipid vesicles. In such an instance, due to the water solubility of the compound or salt, the compound or salt will be substantially entrained within the hydrophilic center or core of the liposomes. The lipid layer employed may be of any conventional composition and may either contain cholesterol or may be cholesterol-free. When the compound or salt of interest is water-insoluble, again employing conventional liposome formation technology, the salt may be substantially entrained within the hydrophobic lipid bilayer which forms the structure of the liposome. In either instance, the liposomes which are produced may be reduced in size, as through the use of standard sonication and homogenization techniques.

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Of course, the liposomal formulations containing the compounds disclosed herein or salts thereof, may be lyophilized to produce a lyophilizate which may be reconstituted with a pharmaceutically acceptable carrier, such as water, to regenerate a liposomal suspension.

The compounds and compositions of the present invention can be administered by any means that transports the active agents to the lung, including but not limited to nasal administration, inhalation, and insufflation. The active agents disclosed herein can be administered to the lungs of a patient by any suitable means, but are preferably administered by generating an aerosol comprised of respirable particles, the respirable particles comprised of the active agents, which particles the subject inhales. The respirable particles can be liquid or solid, and they can optionally contain other therapeutic ingredients, including, but not limited to surfactants.

Particles comprised of active agents for practicing the present invention should be administered as a formulation including particles of respirable size: that is, particles of a size sufficiently small to pass through the nose, mouth and larynx upon inhalation and into the bronchi and alveoli of the lungs. In general, respirable particles range from about 0.5 to 10 microns in diameter. Particles of non-respirable size that are included in the aerosol tend to deposit in the throat and be swallowed. Accordingly, the quantity of non-respirable particles in the aerosol is preferably minimized. For nasal administration, a particle size in the range of 10-500 μm is preferred to ensure retention in the nasal cavity. Alternatively, droplets can be given.

Liquid pharmaceutical compositions of active agents for producing an aerosol can be prepared by combining the active agents with a suitable vehicle, such as sterile pyrogen free water. Other therapeutic compounds can optionally be included.

Solid particulate compositions containing respirable dry particles of micronized active agents can be prepared by grinding dry antisense compound with a mortar and pestle, and then passing the micronized composition through a 400 mesh screen to break up or separate out large agglomerates. A solid particulate composition comprising the active agent can optionally contain a dispersant that serves to facilitate the formation of an aerosol. A suitable dispersant is lactose, which can be blended with the active agents in any suitable ratio e.g., a 1 to 1 ratio by weight.
The aerosols of liquid particles comprising the active agents can be produced by any suitable means, such as with a nebulizer. See e.g., U.S. Pat. No. 4,501,729.

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Nebulizers are commercially available devices which transform solutions or suspensions of the active ingredient into a therapeutic aerosol mist either by means of acceleration of a compressed gas, typically air or oxygen, through a narrow venturi orifice or by means of ultrasonic agitation. Suitable formulations for use in nebulizers consist of the active ingredient in a liquid carrier, the active ingredient comprising up to 40% w/w, but preferably less than 20% w/w, of the formulation. The carrier is typically water or a dilute aqueous alcoholic solution, preferably made isotonic with body fluids by the addition of, for example, sodium chloride. Optional additives include preservatives if the formulation is not prepared sterile, for example, methyl hydroxybenzoate, antioxidants, flavoring agents, volatile oils, buffering agents and surfactants.

The aerosols of solid particles comprising the active agents can likewise be produced with any solid particulate medicament aerosol generator. Aerosol generators for administering solid particulate medicaments to a subject produce particles, which are respirable, as explained above, and generate a volume of aerosol containing a predetermined metered dose of a medicament at a rate suitable for human administration. One illustrative type of solid particulate aerosol generator is an insufflator. Suitable formulations for administration by insufflation include finely comminuted powders that can be delivered by means of an insufflator or taken into the nasal cavity in the manner of a snuff. In the insufflator, the powder, e.g., a metered dose thereof effective to carry out the treatments described herein, is contained in capsules or cartridges, typically made of gelatin or plastic, which are either pierced or opened in situ and the powder delivered by air drawn through the device upon inhalation or by means of a manually-operated pump. The powder employed in the insufflator consists either solely of the active ingredient or of a powder blend comprising the active ingredient, a suitable powder diluent, such as lactose, and an optional surfactant. The active ingredient typically comprises from 0.1 to 100 w/w of the formulation. A second type of illustrative aerosol generator comprises a metered dose inhaler. Metered dose inhalers are pressurized aerosol dispensers, typically containing a suspension or solution formulation of the active ingredient in a liquefied propellant. During use these devices discharge the formulation through a valve adapted to deliver a metered volume, typically from 10 to 150 µl, to produce a fine particle spray containing the active ingredient. Suitable

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propellants include certain chlorofluorocarbon compounds, for example, dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane and mixtures thereof. The formulation can additionally contain one or more co-solvents, for example, ethanol, surfactants, such as oleic acid or sorbitan trioleate, antioxidants and suitable flavoring agents.

The aerosol, whether formed from solid or liquid particles, can be produced by the aerosol generator at a rate of from about 10 to 150 liters per minute, more preferably from about 30 to 150 liters per minute, and most preferably about 60 liters per minute. Aerosols containing greater amounts of medicament can be administered more rapidly.

Any propellant may be used in carrying out the present invention, including both chlorofluorocarbon-containing propellants and non-chlorofluorocarbon-containing propellants. Thus, fluorocarbon aerosol propellants that may be employed in carrying out the present invention including fluorocarbon propellants in which all hydrogens are replaced with fluorine, chlorofluorocarbon propellants in which all hydrogens are replaced with chlorine and at least one fluorine, hydrogen-containing fluorocarbon propellants, and hydrogen-containing chlorofluorocarbon propellants. Examples of such propellants include, but are not limited to: CF_3-CHF-CF_2H; CF_3-CH_2-CF_2H; CF_3-CHF-CF_3; CF_3-CH_2-CF_3; CF_3-CHCl-CF_2Cl; CF_3-CHCl-CF_3; cy-$C(CF_2)_3$-CHCl; CF_3-CHCl-CH_2Cl; CF_3-CHF-CF_2Cl; CF_3-CHCl-CFHCl; CF_3-CFCl-CFHCl; CF_3-CF_2-CF_2H; CF_3-CF_2-CH_3; CF_2H-CF_2-CFH_2; CF_3-CF_2-CFH_2; CF_3-CF_2-CH_2Cl; CF_2H-CF_2-CH_3; CF_2H-CF_2-CH_2Cl; CF_3-CF_2-CF_2-CH_3; CF_3-CF_2-CF_2-CF_2H; CF_3-CHF-CHF-CF_3; CF_3-O-CF_3; CF_3-O-CF_2H; CF_2H-H-O-CF_2H; CF_2H-O-CFH_2; CF_3-O-CH_3; CF_3-O-CF_2-CF_2H; CF_3-O-CF_2-O-CF_3; cy-CF_2-CF_2-O-CF_2-; cy-CHF-CF_2-O-CF_2-; cy-CH_2-CF_2-O-CF_2-; cy-CF_2-O-CF_2-O-CF_2-; CF_3-O-CF_2-Br; CF_2H-O-CF_2-Br; and mixtures thereof, where "cy" denotes a cyclic compound in which the end terminal covalent bonds of the structures shown are the same so that the end terminal groups are covalently bonded together. Particularly preferred are hydrofluoroalkanes such as 1,1,1,2-tetrafluoroethane (propellant 134a) and heptafluoropropane (propellant 227). A stabilizer such as a fluoropolymer may optionally be included in formulations of fluorocarbon propellants, such as described in U.S. Patent No. 5,376,359 to Johnson, the disclosure of which is incorporated herein by reference in its entirety.

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Other pharmaceutical compositions may be prepared from the water-insoluble compounds disclosed herein, or salts thereof, such as aqueous base emulsions. In such an instance, the composition will contain a sufficient amount of pharmaceutically acceptable emulsifying agent to emulsify the desired amount of the compound or salt thereof. Particularly useful emulsifying agents include phosphatidyl cholines, and lecithin.

In addition to compounds of Formula I and II, A_1 adenosine receptor antagonists or P_{2x} purinoceptor antagonists, or their salts, the pharmaceutical compositions may contain other additives, such as pH-adjusting additives. In particular, useful pH-adjusting agents include acids, such as hydrochloric acid, bases or buffers, such as sodium lactate, sodium acetate, sodium phosphate, sodium citrate, sodium borate, or sodium gluconate. Further, the compositions may contain microbial preservatives. Useful microbial preservatives include methylparaben, propylparaben, and benzyl alcohol. The microbial preservative is typically employed when the formulation is placed in a vial designed for multidose use. Of course, as indicated, the pharmaceutical compositions of the present invention may be lyophilized using techniques well known in the art.

4. Dosage and routes of administration.

As noted above, the present invention provides pharmaceutical formulations comprising the active compounds (including the pharmaceutically acceptable salts thereof), in pharmaceutically acceptable carriers for oral, rectal, topical, buccal, parenteral, intramuscular, intradermal, or intravenous, transdermal, intraarticular, nasal, and inhalational administration.

According to the present invention, methods of this invention comprise administering an effective amount of a composition of the present invention as described above to the subject. The effective amount of the composition, the use of which is in the scope of present invention, will vary somewhat from subject to subject, and will depend upon factors such as the age and condition of the subject and the route of delivery. Such dosages can be determined in accordance with routine pharmacological procedures known to those skilled in the art. For example, the compounds of the present invention can be administered to the subjeet in an amount ranging from a lower limit from about 0.01, 0.05, 0.10, 0.50, 1.0, 5.0, or 10% to an

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upper limit ranging from about 10, 20, 30, 40, 50, 60, 70, 80, 90, 95, 96, 97, 98, 99, or 100% by weight of the composition. In some embodiments, the compounds comprise from about 0.05 to about 95% by weight of the composition. In other embodiments, the compounds comprise from about 0.05 to about 60% by weight of the composition. In still other embodiments, the compounds comprise from about 0.05 to about 10% by weight of the composition.

The therapeutically effective dosage of any specific compound will vary somewhat from compound to compound, patient to patient, and will depend upon the eondition of the patient and the route of delivery. As a general proposition, a dosage from about 0.1 to about 50 mg/kg will have therapeutic efficacy, with still higher dosages potentially being employed for oral administration, wherein aerosol administration is usually lower than oral or intravenous administration. Toxicity concerns at the higher level may restrict intravenous dosages to a lower level such as up to about 10 mg/kg, all weights being calculated based upon the weight of the active base, including the cases where a salt is employed. Typically a dosage from about 0.5 mg/kg to about 5 mg/kg will be employed for intravenous or intramuscular administration. A dosage from about 10 mg/kg to about 50 mg/kg may be employed for oral administration.

In particular embodiments, administration to a subject such as a human, a dosage of from about 0.01, 0.1, or 1 mg/kg up to 50, 100, or 150 mg/kg or more for each active agent can be employed. Depending on the solubility of the particular formulation of active compounds administered, the daily dose can be divided among one or several unit dose administrations. The administration of the active compounds can be carried out therapeutically (i.e., as a rescue treatment) or prophylactically.

The present invention is explained in greater detail in the following non-limiting Examples.

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EXAMPLE 1

In vitro pharmacology studies performed support the finding that the A_1 receptor antagonists of the present invention have a high affinity for the human A_1 AR (0.58 μM). The protein source for the human A1 ARs in these pharmacological studies was obtained from membranes from human pulmonary artery endothelial cells purchased from BioWhittaker Inc. (Walkersville, MD). This protein source for the human A_1 AR was not obtained from a cell line transfected with a recombinant human A_1 AR. As shown below in Table 1, the pharmacology studies demonstrate that the affinity of the compounds as antagonists for the human A_1 AR (L-97-1) is approximately 3 – 10 times that of bamiphylline which binds to human A_{2a} AR.

TABLE 1 Affinities of L-97-1 and other adenosine receptor ligands for Human A1 adenosine receptc

Ligand	Human A_1 (^{125}I-BWA844U)				Human A_1 (^{3}H-DPCPX)		
	IC_{50} (μM)	K_i (μM)	IC_{50} (μg/ml)	N	IC_{50} (μM)	K_i (μM)	IC_{50} (μg/ml)
L-97-1	2.077 0.712	1.13 ± 0.39	1.077 ± 0.369	3	1.421 ± 0.567	0.580 ± 0.330	0.737 ± 0.294
Bamiphylline	20.150 ± 12.65	11.05 ± 6.95	8.483 ± 5.325	2	3.770 ± 0.964	1.927 ± 0.517	1.587 ± 0.406
DPCPX	13.2 ± 1.2	7.19 ± 0.654	4.013 ± 0.365	3	0.076 ± 0.036	0.038 ± 0.018	0.023 ± 0.011
CCPA					0.034 ± 0.023	0.017 ± 0.012	0.013 ± 0.009

Bamiphylline binds to the human A_{2a} AR (27 μM). L-97-1 does not bind to the human A_{2a} AR (>100 μM). Neither L-97-1 (> 100 μM) nor bamiphylline (> 100 μM) bind to the human A_{2b} AR.

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EXAMPLE 2

In vitro pharmacology studies performed support the finding that the A_1 receptor antagonists of the present invention are highly selective for the human A_1 adenosine receptor versus human A_{2a} and A_{2b} ARs and the rat A_3 AR as shown in the table below.

TABLE 2 Affinities of L-97-1 and other adenosine receptor ligands for Human A2a, A2b, and Rat A3 adenosine receptor subtypes

Ligand	Human A_{2a} (^{3}H-CGS21680)			Human A_{2b} (^{3}H-DPCPX)			Rat A_3 (^{125}I-AB-MECA)		
	IC_{50} (μM)	K_i (μM)	N	IC_{50} (μM)	K_i (μM)	N	IC_{50} (μM)	K_i (μM)	N
L-97-1	> 100		3	> 100		3	67.33 ± 28.76		3
Bamiphylline	26.6 ± 7.9	12.92 ± 3.85	2	> 100		3	36.6 ± 4.00	17.55 ± 1.95	2
DPCPX				0.219 ± 0.065	0.12 ± 0.035	3			
CGS-21680	0.32 ± 0.215	0.158 ± 0.106	3						
Cl-IB-MECA							0.19 nM	0.09 nM	1

EXAMPLE 3

A feline model of acute lung injury following endotoxin administration was employed to study the effects of the A_1 adenosine receptor antagonist, bamiphylline (BAM), or P_{2x} antagonist, PPADS, on alveolar inflammatory cells, red blood cells, edema, and injury index in lungs after endotoxin treatment.

BAM was dissolved in 0.9% saline at 2 to 4 mg/ml and administered at 10 mg/kg/hr as a continuous intravenous infusion during and for 30 minutes to cats after the endotoxin infusion (Group II, n=5). PPADS was administered at 15 mg/kg as an intravenous bolus 30 minutes before administration of the endotoxin (Group III, n=5). In addition, a combination of PPADS (15 mg/kg, i.v. prior to endotoxin administration) and BAM (10 mg/kg/hr, continuous intravenous infusion 30 minutes prior to and throughout endotoxin until 1 hour post endotoxin) was administered (Group IV, n=5). E. coli endotoxin (Sigma Chemical Com., St. Louis, Mo.) was dissolved in 0.9% saline at 2.5 mg/ml. The endotoxin (15 mg/kg) was administered to treated groups and to a group of untreated cats (Group I, n=5) as a continuous intralobar infusion over 30 to 40 minutes into the left lower lobe. In control animals

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(Group V, n=5), the lower left lobe was perfused for one hour only with blood drawn from the aorta. Two hours after completion of the endotoxin infusion, the cats received an overdose of pentobarbital (50 mg/kg) and the left lower lobe was perfusion fixed *in situ* and the lung specimens were analyzed as described in U.S. Patent No. 6,001,842 in Example 4. The results are shown below in Table 3.

Table 3.

Treatment groups	PMN[1]		Macro[1]		RBC[1]		Edematous alveoli %	Injured[2] alveoli %
	Alv %	#/alv	alv %	#/alv	Alv %	#/alv		
I Endotoxin (n=5)	25±9*	0.33±0.14*	26±12*	0.38±0.19*	50±3.2*	2.03±1.24*	22±17*	57±31*
II BAM + EN (n=5)	8±4	0.11±0.07	7±4	0.09±0.05	14±4†	0.56±0.51	5±3†	21±14†
III PPADS + EN (n=5)	9±4	0.10±0.04	8±3	0.10±0.04	6±3	0.13±0.09	1±1	7±3
IV BAM+PPADS + EN (n=5)	7±3	0.08±0.04	8±6	0.17±0.23	8±4	0.22±0.12	0.3±0.6	6±4
V Control (n=5)	6±3	0.06±0.04	6±3	0.09±0.08	7±2	0.11±0.05	0.3±0.5	5±4

Means and standard deviations: n = number of cats.

[1]Alv(%) = percent alveoli containing two or more cells; #/alv = average number of cells per alveolus;

[2]Average percent alveoli with two or more inflammatory cells or RBC, or edematous fluid; Group I: endotoxin (EN) treatment, 15 mg/kg i.v.; II: BAM, i.v., continuous infusion 30 min. prior to and throughout EN until 30 min. post EN; III: PPADS, i.v., 30 min. prior to EN; IV: combined PPADS and BAM treatment; V: control, 1 hour arterial perfusion only.

*Significantly different from all EN groups with A_1 adenosine receptor antagonist and P_{2x} antagonist treatment (groups II, III and IV), and control; ANOVA and Bonferroni range test, at $p \leq 0.05$; % data were arcsin transformed.

†Group II given BAM only had higher numbers of alveoli containing RBC, edematous alveoli, and injured alveoli, compared with groups III and IV given PPADS, using Student's t-test for unpaired data at $p \leq 0.05$.

EXAMPLE 4

Hemodynamic measurements, including mean lobar arterial, femoral arterial, and left atrial pressures were obtained before endotoxin infusion (baseline), during endotoxin infusion and two hours following initiation of the endotoxin infusions. Data were analyzed and summarized in Table 4 below. These studies show that BAM and PPADS combined have a greater effect on endotoxin-induced hypotension (i.e., shock following intralobar administration of endotoxin) than either treatment alone.

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Table 4.

Pressures	Group I	Group II	Group III	Group IV	Group V
Lobar Arterial	(n=5)	(n=5)	(n=5)	(n=5)	(n=5)
Baseline	5.7±2.1	3.8±0.7	3.2±1.0	4.4±1.1	5.6±2.0
5' after endotoxin	5.7±1.4	6.0±1.6	5.9±1.2	6.0±0.6	
15' after endotoxin	6.3±1.9	5.2±1.1	5.6±0.7	5.3±0.6	
30' after endotoxin	6.3±2.0	3.8±0.2	4.4±0.8	4.2±0.5	
60' after endotoxin	5.4±1.6	4.2±0.5	3.6±1.2T	5.3±0.5	7.0±1.4
120' after endotoxin	7.0±2.1	5.7±1.5	4.6±2.2	5.1±1.2	
Femoral Arterial	(n=5)	(n=5)	(n=5)	(n=5)	(n=5)
Baseline	131±10.4	147±11.5	139±4.9	137±11	131±2.4
5' after endotoxin	106±6.8	115±5.2*	123±8.5	121±8.4	
15' after endotoxin	105±3.5	107±3.7*	120±9.5	120±9.6	
30' after endotoxin	89±6.8*	103±2.5*	114±9.7	116±7.3	
60' after endotoxin	85±10.7*T	107±6.6*T	106±6.6*T	114±8.0T	134±7.0
120' after endotoxin	87±11.2*	111±7.3*	111±10.8*	120±7.6	
Left atrial	(n=5)	(n=5)	(n=5)	(n=4)	(n=2)
Baseline	0.6±0.4	1.1±0.8	0.9±0.6	1.3±1.0	1.5±1.5
5' after endotoxin	1.1±0.7	0.2±0.2	1.7±1.4	0.9±0.6	
15' after endotoxin	1.3±0.8	0.6±0.4	1.0±1.0	0.1±0.1	
30' after endotoxin	1.3±0.9	0.7±0.4	0.6±0.6	0	
60' after endotoxin	0.8±0.8	0.6±0.6	0.1±0.1	0	0.5±0.5
120' after endotoxin	0.5±0.3	2.0±1.5	0.2±0.2	0	

Data expressed as mean ± SEM; n = number of animals; Group I, endotoxin (15 mg/kg, i.a.); Group II, endotoxin (15 mg/kg, i.a.) + BAM continuous infusion (10 mg/kg/hr, IV) 30 min. before, during and after endotoxin; Group III, endotoxin (15 mg/kg, i.a.) + PPADS (15 mg/kg, IV) 30 minutes before endotoxin; Group IV, endotoxin (15 mg/kg, i.a.) + PPADS (15 mg/kg, IV) 30 minutes before + BAM 30 minutes before, during and after endotoxin; Group V, controls l-h perfusion only.

*Different compared with baseline within a group using Student's t-test with Bonferroni correction ($p<0.05$).

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T Different compared with Group V at the same time with use of ANOVA with Bonferroni correction ($p<0.05$).

The foregoing is illustrative of the present invention, and is not to be construed as limiting thereof. The invention is defined by the following claims, with equivalents of the claims to be included therein.

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That Which is Claimed is:

1. A method of treating a purinoceptor-related disorder in a subject in need thereof, comprising concurrently administering *(a)* an A_1 adenosine receptor antagonist or a P_{2x} purinoceptor antagonist with *(b)* an at least one additional active agent effective to treat said purinoceptor-related disorder.

2. The method according to claim 1, wherein the purinoceptor-related disorder is an inflammatory disorder.

3. The method according to claim 1, wherein the purinoceptor-related disorder is selected from the group consisting of congestive heart failure, systemic hypertension, pulmonary hypertension, ischemia-reperfusion organ injury, endotoxin-related tissue injury, anaphylactic shock, allergic rhinitis, Alzheimer's disease, depression, obesity, asthma, diabetes, cystic fibrosis, allergic conditions, autoimmune disorders, chronic obstructive pulmonary disorders, chronic cough, coronary artery disease, biliary colic, fibrosis, sclerosis, renal failure, adult respiratory distress syndrome (ARDS), Severe Acute Respiratory Syndrome (SARS), Acute Lung Injury (ALI), septicemia, substance abuse, drug dependence, and Parkinson's disease.

4. The method according to claim 1, wherein the purinoceptor related disorder is asthma.

5. The method according to claim 4, wherein the asthma is intrinsic asthma.

6. The method according to claim 4, wherein the asthma is extrinsic asthma.

7. The method according to claim 1, wherein the purinoceptor-related disorder is septicemia.

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8. The method according to claim 1, wherein the purinoceptor-related disorder is an autoimmune disorder.

9. The method according to claim 1, wherein the purinoceptor-related disorder is coronary artery disease.

10. The method according to claim 1, wherein the at least one additional active agent effective to treat said purinoceptor-related disorder is selected from the group consisting of steroids, beta-2 agonists, xanthines, A_1 adenosine receptor antagonists, A_{2a} adenosine receptor agonists, A_{2b} adenosine receptor antagonists, A_3 adenosine receptor antagonists, P_{2y} purinoceptor agonists, P_{2x} purinoceptor antagonists, TNF alpha mAb, TNF alpha antagonists, selectin antagonists, beta-2 integrin blockers, interferon, disease modifying anti-rheumatic drugs (DMARDs), proteasome inhibitors, VAP-1 mAb, rNIF, immunomodulators, NHE inhibitors, monophosphoryl Lipid A (MPL A), mycobacterium, endotoxin, interferon-alpha, granulocyte colony stimulating factor (GCSF), granulocyte-macrophage colony stimulating factor (GMCSF), endotoxin antagonists, antifactor IX mAb, p38 MAPK inhibitor, lipid emulsion, re PAF acetylhydrolase, CD14 receptor antagonist, caspase inhibitors, protease inhibitors, nitric oxide scavengers, nitric oxide blockers, nitric oxide synthetase inhibitors, re tissue factor protein inhibitors (re TFPI), bactericidal permeabilizing increasing re (BPI) protein fragment, CpG DNA, Mycobacterium vaccae, lactobacillus, modified endotoxin – Lipid A, diuretics, vasodilators, anti-platelet agents, anticoagulants, nitrates, calcium channel blockers, beta receptor antagonists, antihypertensives, diuretics, antidepressants, appetite suppressants, mast cell stabilizers, anti-histamines, cetirizine, leukotriene receptor antagonists, anticytokines, phosphodiesterase enzyme inhibitors, 5-lipoxygenase inhibitors, platelet activating factor antagonists, thromboxane receptor antagonists, neurokinin receptor antagonists, central nervous system (CNS) stimulants, cognition enhancers, acetylcholinesterase inhibitors, acridine derivatives, complement receptor antagonists, cyclosporin, endothelin receptor antagonists, angiotensin enzyme converting (ACE) inhibitors, antisense oligonucleotides, anti-IgE, insulin, oral hypoglycemics, smooth muscle relaxants, antibiotics, antiviral agents, antifungal agents, anti-inflammatory

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agents, cancer therapies, narcotics, antitussive agents, surfactants, and combinations thereof.

11. The method according to claim 1, wherein the at least one additional aetive agent effective to treat the purinoceptor-related disorder is selected from the group consisting of fluticasone, salmeterol, theophylline, and combinations, thereof.

12. The method according to claim 1, wherein the at least one additional active agent effective to treat the purinoceptor-related disorder is selected from the group consisting of A_1 adenosine receptor antagonists, A_{2a} adenosine receptor agonists, A_{2b} adenosine receptor antagonists, A_3 adenosine receptor antagonists, P_{2y} purinoceptor agonists, P_{2x} purinoceptor antagonists, and combinations thereof.

13. The method according to claim 1, wherein the at least one additional active agent effective to treat the purinoceptor-related disorder is an at least one bronchodilating agent.

14. The method according to claim 1, wherein the at least one additional active agent effective to treat the purinoceptor-related disorder is an at least one anti-inflammatory agent.

15. The method according to claim 1, wherein the at least one additional active agent effective to treat the purinoceptor-related disorder is at least one agent useful for the prevention or treatment of coronary artery disease.

16. The method according to claim 1, wherein the administering step comprises inhalation therapy.

17. The method according to claim 1, wherein the administering step comprises oral administration.

18. The method according to claim 1, wherein the A_1 adenosine receptor antagonist comprising a compound of Formula I:

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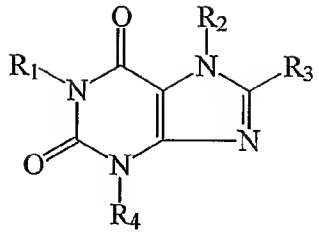
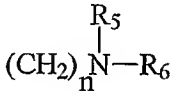
(I)



wherein

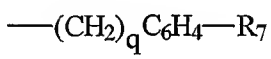
R_1 is selected from the group consisting of C_1-C_8 alkyl;

R_2 is of the formula:



wherein n is an integer ranging from 1 to 8; R_5 is H or $CH_3(CH_2)_p$, wherein p is an integer ranging from 1 to 7; and R_6 is H or $(CH_2)_mOH$, wherein m is an integer ranging from 1 to 8;

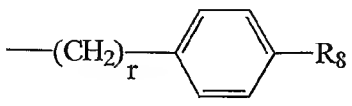
R_3 is of the formula:



and

wherein q is an integer ranging from 1 to 8; and wherein R_7 is selected from the group consisting of H, NH_2, R_9COOH, wherein R_9 is an alkylene or alkenylene group having 1 to 8 carbon atoms, and $(CH_2)_tOH$, wherein t is an integer ranging from 1 to 8; and

R_4 is of the formula:



wherein R_8 is selected from the group consisting of H; NH_2; $(CH_2)_sOH$, wherein s is an integer ranging from 1 to 8; and $R_{10}COOH$, wherein R_{10} is an alkylene

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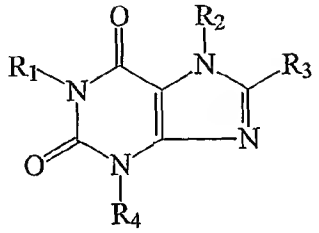
or alkenylene group having 1 to 8 carbon atoms; and r is an integer ranging from 1 to 8, or a pharmaceutically acceptable salt thereof, or a P_{2x} purinoceptor antagonist or a pharmaceutically acceptable salt thereof.

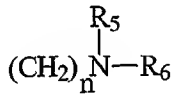
19. The method according to claim 18, wherein the A_1 adenosine receptor antagonist comprises a compound of Formula II:

(II)



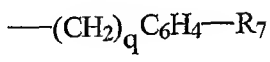
wherein R_1 is C_3 alkyl;

R_2 is of the formula:



wherein n is 2; R_5 is $CH_3(CH_2)_p$, wherein p is 1; R_6 is $(CH_2)_mOH$, wherein m is 2;

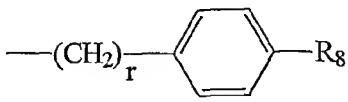
R_3 is of the formula:



and

wherein q is 1; R_7 is H; and

R_4 is of the formula:



wherein R_8 is NH_2; and r is 2; or

a pharmaceutically acceptable salt thereof.

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20. The method according to claim 18, wherein the purinoceptor-related disorder is an inflammatory disorder.

21. The method according to claim 18, wherein the purinoceptor-related disorder is selected from the group consisting of congestive heart failure, systemic hypertension, pulmonary hypertension, ischemia-reperfusion organ injury, endotoxin-related tissue injury, anaphylactic shock, allergic rhinitis, Alzheimer's disease, depression, obesity, asthma, diabetes, cystic fibrosis, allergic conditions, autoimmune disorders, chronic obstructive pulmonary disorders, chronic cough, coronary artery disease, biliary colic, fibrosis, sclerosis, renal failure, adult respiratory distress syndrome (ARDS), Severe Acute Respiratory Syndrome (SARS), Acute Lung Injury (ALI), septicemia, substance abuse, drug dependence, and Parkinson's disease.

22. The method according to claim 18, wherein the purinoceptor-related disorder is asthma.

23. The method according to claim 22, wherein the asthma is intrinsic asthma.

24. The method according to claim 22, wherein the asthma is extrinsic.

25. The method according to claim 18, wherein the purinoceptor-related disorder is septicemia.

26. The method according to claim 18, wherein the purinoceptor-related disorder is an autoimmune disorder.

27. The method according to claim 18, wherein the purinoceptor-related disorder is coronary artery disease.

28. The method according to claim 18, wherein the at least one additional active agent effective to treat the purinoceptor-related disorder is selected from the group consisting of steroids, beta-2 agonists, xanthines, A_1 adenosine receptor

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antagonists, A_{2a} adenosine receptor agonists, A_{2b} adenosine receptor antagonists, A_3 adenosine receptor antagonists, P_{2y} purinoceptor agonists, P_{2x} purinoceptor antagonists, TNF alpha mAb, TNF alpha antagonists, selectin antagonists, beta-2 integrin blockers, interferon, disease modifying anti-rheumatic drugs (DMARDs), proteasome inhibitors, VAP-1 mAb, rNIF, immunomodulators, NHE inhibitors, monophosphoryl Lipid A (MPL A), mycobacterium, endotoxin, interferon-alpha, granulocyte colony stimulating factor (GCSF), granulocyte-macrophage colony stimulating factor (GMCSF), endotoxin antagonists, antifactor IX mAb, p38 MAPK inhibitor, lipid emulsion, re PAF acetylhydrolase, CD14 receptor antagonist, caspase inhibitors, protease inhibitors, nitric oxide scavengers, nitric oxide blockers, nitric oxide synthetase inhibitors, re tissue factor protein inhibitors (re TFPI), bactericidal permeabilizing increasing re (BPI) protein fragment, CpG DNA, Mycobacterium vaccae, lactobacillus, modified endotoxin – Lipid A, diuretics, vasodilators, anti-platelet agents, anticoagulants, nitrates, calcium channel blockers, beta receptor antagonists, antihypertensives, diuretics, antidepressants, appetite suppressants, mast cell stabilizers, anti-histamines, cetirizine, leukotriene receptor antagonists, anticytokines, phosphodiesterase enzyme inhibitors, 5-lipoxygenase inhibitors, platelet activating factor antagonists, thromboxane receptor antagonists, neurokinin receptor antagonists, central nervous system (CNS) stimulants, cognition enhancers, acetylcholinesterase inhibitors, acridine derivatives, complement receptor antagonists, cyclosporin, endothelin receptor antagonists, angiotensin enzyme converting (ACE) inhibitors, antisense oligonucleotides, anti-IgE, insulin, oral hypoglycemics, smooth muscle relaxants, antibiotics, antiviral agents, antifungal agents, anti-inflammatory agents, cancer therapies, narcotics, antitussive agents, surfactants, and combinations thereof.

29. The method according to claim 18, wherein the at least one additional active agent effective to treat the purinoceptor-related disorder is selected from the group consisting of fluticasone, salmeterol, theophylline, and combinations, thereof.

30. The method according to claim 18, wherein the at least one additional active agent effective to treat the purinoceptor-related disorder is selected from the group consisting of A_1 adenosine receptor antagonists, A_{2a} adenosine receptor

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agonists, A_{2b} adenosine receptor antagonists, A_3 adenosine receptor antagonists, P_{2y} purinoceptor agonists, P_{2x} purinoceptor antagonists, and combinations thereof.

31. The method according to claim 18, wherein the at least one additional active agent effective to treat the purinoceptor-related disorder is an at least one bronchodilating agent.

32. The method according to claim 18, wherein the at least one additional active agent effective to treat the purinoceptor-related disorder is an at least one anti-inflammatory agent.

33. The method according to claim 18, wherein the at least one additional active agent effective to treat the purinoceptor-related disorder is an agent useful for the prevention or treatment of coronary artery disease.

34. The method according to claim 18, wherein the purinoceptor-related disorder is Alzheimer's disease and the at least one additional active agent effective to treat the purinoceptor-related disorder is selected from the group consisting of cognition enhancers and anti-inflammatory agents, and combinations thereof.

35. The method according to claim 18, wherein the administering step comprises inhalation therapy.

36. The method according to claim 18, wherein the administering step comprises oral administration.

37. A method of treating coronary artery disease comprising administering an A_1 adenosine receptor antagonist or a P_{2x} purinoceptor antagonist in combination with at least one additional active agent selected from the group consisting of nitrates, calcium channel blockers, beta blockers, anticoagulants, and combinations thereof.

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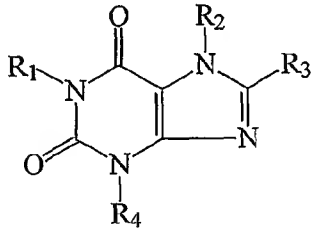
38. A method of treating asthma comprising administering an A_1 adenosine receptor antagonist or a P_{2x} purinoceptor antagonist in combination with at least one additional active agent selected from the group consisting of A_1 adenosine receptor antagonists, A_{2a} adenosine receptor agonists, A_{2b} adenosine receptor antagonists, A_3 adenosine receptor antagonists, P_{2y} purinoceptor agonists, P_{2x} purinoceptor antagonists, leukotriene receptor antagonists, anticytokines, phosphodiesterase enzyme inhibitors, histamine antagonists, and combinations thereof.

39. A method of treating autoimmune disorders comprising administering an A_1 adenosine receptor antagonist or a P_{2x} purinoceptor antagonist in combination with at least one additional active agent selected from the group consisting of anti-inflammatory agents, antibiotic agents, antiviral agents, and P_{2y} purinoceptor agonists.

40. The method according to claim 37, 38, or 39, wherein the A_1 adenosine receptor antagonist comprises a compound of Formula I:

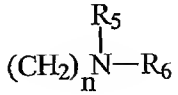
(I)



wherein

R_1 is selected from the group consisting of C_1-C_8 alkyl;

R_2 is of the formula:



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wherein n is an integer ranging from 1 to 8; R_5 is H or $CH_3(CH_2)_p$, wherein p is an integer ranging from 1 to 7; and R_6 is H or $(CH_2)_mOH$, wherein m is an integer ranging from 1 to 8;

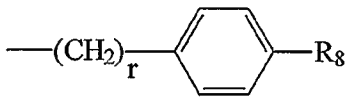
R_3 is of the formula:

$$—(CH_2)_qC_6H_4—R_7$$

and

wherein q is an integer ranging from 1 to 8; and wherein R_7 is selected from the group consisting of H, NH_2, R_9COOH, wherein R_9 is an alkylene or alkenylene group having 1 to 8 carbon atoms, and $(CH_2)_tOH$, wherein t is an integer ranging from 1 to 8; and

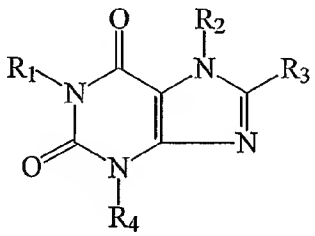
R_4 is of the formula:



wherein R_8 is selected from the group consisting of H; NH_2; $(CH_2)_sOH$, wherein s is an integer ranging from 1 to 8; and $R_{10}COOH$, wherein R_{10} is an alkylene or alkenylene group having 1 to 8 carbon atoms; and r is an integer ranging from 1 to 8, or a pharmaceutically acceptable salt thereof.

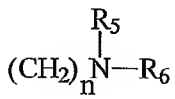
41. The method according to claim 40, wherein the A_1 adenosine receptor antagonist comprises a compound of Formula II:

(II)



wherein R_1 is C_3 alkyl;

R_2 is of the formula:



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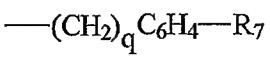
wherein n is 2; R_5 is $CH_3(CH_2)_p$, wherein p is 1; R_6 is $(CH_2)_mOH$, wherein m is 2;

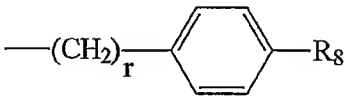
R_3 is of the formula:



and

wherein q is 1; R_7 is H; and

R_4 is of the formula:



wherein R_8 is NH_2; and r is 2; or

a pharmaceutically acceptable salt thereof.

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